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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,451	10/24/2000	Brenda F. Baker	ISPH-0518	2604

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EXAMINER

SCHULTZ, JAMES

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 01/03/2003

b

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/695,451

Applicant(s)

BAKER ET AL.

Examiner

J. Douglas Schultz

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-- **Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --**
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of tumor necrosis factor receptor 1 (TNFR1) expression *in vitro*, and for the antisense-mediated protection against LPS/GalN induced death in a toxic shock mouse model, does not reasonably provide enablement for antisense-mediated inhibition of TNFR1 expression in all whole animals including humans *in vivo*, or for methods of treating diseases associated with its expression in all whole animals including humans *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of TNFR1 in mouse or human cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of TNFR1. The claims of the above invention are also drawn to methods of treating any animal including humans having a condition associated with TNFR1, wherein said compositions are administered to any animal such that expression of

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TNFR1 is inhibited, wherein said condition may be a liver disease including hepatitis, or liver injury, or wherein said condition may be a hyperproliferative disorder including liver cancer. The language of said claims encompasses both *in vivo* whole animal and *in vitro* activity in all animals. The specification teaches a method of using the claimed compositions to inhibit the expression of TNFR1 in cells *in vitro* and for antisense-mediated protection against LPS/GalN induced death in a toxic shock mouse model.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in all animals including humans *in vivo*. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compounds in all animals *in vivo* based solely on its performance *in vitro* or from a derived mouse model is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs in methods of inhibition or treatment in all animals including humans *in vivo*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the art: “gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable” (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, “it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that “internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules” (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column). Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above, in all animals including humans.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of TNFR1 expression *in vitro* or the antisense-mediated protection against LPS/GalN induced death in a toxic shock mouse model as being correlative or representative of the successful *in vivo* use of antisense compounds in all animals, or treatment of any and/or all conditions or diseases suspected of being associated with TNFR1 expression. This is particularly true in view of the lack of guidance in the specification regarding specific compounds, dosage, and administration schedules for a representative number of animal species, and the known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or diseases suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects

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provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to methods of treating or preventing any condition or disease suspected of being associated with TNFR1 expression in all animals including humans. The quantity of experimentation required to practice the invention as claimed in all animals *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered for each species, and most importantly, that target sites in appropriate cells and /or tissues harboring TNFR1 expression such that all harmful expression is inhibited, and that healthy expression is permitted appropriately *in vivo*. Further, treatment and/or preventive effects would need to be verified through experimentation for a representative number of species, to ensure that said treatment is provided for in any or all animals in regards to any and/or all diseases or conditions suspected of being associated with TNFR1 expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with TNFR1 expression in animals including humans, or their tissues or cells, other than that demonstrated in the mouse knockout model, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ojwang et al. (Biochemistry 1997, 36:6033-6045), in view of Baracchini et al. (U.S. Patent Number 5,801,154).

The invention of the above listed claims is drawn to antisense compounds that target nucleobases 727-1310 of TNFR1 and inhibit its expression, wherein said compounds may

comprise internucleoside, sugar or nucleobase modifications, or wherein said compounds may be chimeric or comprise pharmaceutical compositions.

Ojwang et al. teach antisense compounds that are targeted to and inhibit the expression of TNFR1, wherein said compounds comprise phosphorothioate (internucleoside), 2'-O methyl (sugar), or C-5 propynyl (nucleobase) modifications, chimeras, and pharmaceutical (liposome) preparations.

Ojwang et al. does not teach TNFR1 antisense oligos that target the specific nucleobase positions 727-1310, or wherein the sugar and nucleobase moieties comprise 2'-methoxyethyl and 5-methylcytosine modifications respectively.

Baracchini et al. teach sugar and nucleobase moieties comprising 2'-methoxyethyl and 5-methylcytosine modifications respectively.

It would have been obvious for one of ordinary skill in the art to target the above listed region of TNFR1, and to incorporate modifications as taught by Baracchini et al. into the antisense compounds of Ojwang et al. One would have been motivated to target said region with antisense compounds as taught by Baracchini et al., because Baracchini et al. teach that the coding region of a mRNA transcript, of which the instantly claimed region is a part of, is a desirable region to target for gene inhibition. Further motivation to modify the antisense oligos as instantly claimed is provided by Ojwang et al., who indicates the desirability of modifying antisense oligos to increase resistance to degradation by incorporating several modifications that increased the bioactivity of their antisense oligo sequences, and by Baracchini et al., who further teach that such modifications increase an antisense compound's cellular uptake, target affinity

and resistance to degradation. One of ordinary skill in the art would have been motivated to create such compounds to increase bioactivity because Ojwang et al. also teach that TNFR1 is a mediator of inflammation, and that it is an attractive target for intervention in both acute and chronic inflammatory diseases. Finally, one would have a reasonable expectation of success given that Baracchini et al. teach the methods of formulation and successful use of such modified antisense compounds, and since the steps of formulation as outlined by Baracchini et al. are routinely performed by those of skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 1, 2, and 5-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,007,995.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11 of U.S. Patent No. 6,007,995 are drawn to specific sequences which anticipate the above-listed claims of the instant application.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz
December 27, 2002



ANDREW WANG
SUPERVISORY PATENT EXAMINER
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